Hypolipidemic drugs

- Also called antihyperlipidemic drugs, antihyperlipoprotinemic drugs.
  main points:
  - Metabolism of lipids in general
  - Site of action of the drugs
  - Classification of the drugs
  - The main effects of these drugs
  - In general, Antihyperlipidemic drugs reduce levels of lipids and lipoproteins in blood, and they are considered as very important drugs because they prevent cardiovascular disease, e.g. myocardial infarction, stroke or any occlusion and thrombus, by slowing the accelerated atherosclerosis in hyperlipidimic individual.
  - Lipids, in general, are very important when they are taken in reasonable amounts and they are two types:-
  1) triglycerides.
  2) cholesterol.
  - Cholesterol is very important for cell membrane and for formation of hormones, steroids and so on for our body.

- Triglycerides are composed of glycerol and three fatty acids and is important for the energy in muscle and fat.
-The concentration of cholesterol in the cells depends usually on how much is synthesized in the body and how much is taken from outside.
-If the concentration of the cholesterol in the cells (in liver or any tissue) decreases, the cells will increase the synthesis of LDL receptors that attach LDL from the blood because LDL is the transporter of cholesterol, so decrease LDL levels in the blood. This is the main point for the relation between the concentration of cholesterol in the cells and LDL and cholesterol in the blood.
-If there is a high amount of cholesterol because of increased intake, so there is no synthesis of cholesterol , no synthesis of LDL receptors, so increase LDL in blood, so we'll have hypercholesterolemia carried by LDL transporter , then it deposits in tissue and macrophage come and make the foam cell and start the formation of atheroma.

- **Absorption and metabolism of lipids:-**

- Dietary lipids or fats are taken up from the outside and then in the intestine they are absorbed with the help of bile acids , which is formed from cholesterol. In the intestinal cells, these triglycerides are incorporated into lipoproteins and apoproteins, and forms the transporter form of lipids or chylomicron. Chylomicron is formed of core and periphery, the core is composed of dietary triglycerides and cholesterol ester and in the periphery there is free cholesterol, phospholipids and apoproteins (apoproteins are proteins that binds to the receptors and distinguish LDL from HDL and so on).
- After chylomicron is produced in the intestine, it is transported into the blood through the thoracic duct along with the lymph. In the blood, during the passage in the capillary, in the capillary endothelium there is an enzyme called lipoprotein lipase, which changes chylomicron into chylomicron remnant because it degrades triglycerides transforming them into free fatty acids and glycerol(free fatty acids are taken into the

muscle, and fat tissue for formation of triglyceride again, and glycerol is going into the liver).
- chylomicron is changed to chylomicron remnant, with specific apoprotein. Chylomicron remnant has less triglycerides but low or no cholesterol ester, and is taken up by the liver by its receptors and give cholesterol out. Cholesterol is important in the liver because it is a fuel for many things i.e. steroid hormones, bile acids and VLDL.
- VLDL is released from the liver, this VLDL carry endogenous triglycerides. So we have 2 transporters of triglycerides, exogenous TG by chylomicron and endogenous TG by VLDL. then VLDL will go into circulation in the capillaries there is the lipoprotein lipase that change VLDL into IDL by decreasing its TG content, and in the same manner IDL (short lived) is converted into LDL, the most atherogenic lipid.
- During this conversion VLDL losses triglycerides along with a part of the surface which is cholesterol and this cholesterol is removed by HDL.
- HDL mainly collects cholesterol and take it to the liver for degradation, not only cholesterol from this conversion but also cholesterol from the tissue.

- **Classes:-**

1) Chylomicron, transporter of dietary triglycerides.
2) Chylomicron remnant, mainly cholesterol and takes it into the liver.
3) IDL.
4) VLDL, transporter of endogenous TG.
5) LDL, transporter of cholesterol to all cells.
6) HDL takes cholesterol from cells.

- The aim of treatment is to increase HDL and decrease LDL.

- **Types of disease:-**

- Primary and secondary hyperlipidemia, endogenous or exogenous increase in one of the lipoproteins and the most important and common is (III, IV, V) hypertriglecridemia , i.e. triglycerides are high. We use fibrates drugs to treat these patients.

- Mixed triglycerides and cholesterol (I, II, III) statins like sulfastatin are the most important drugs that is used for all types of lipids in all hyperlipidemic states.
- So we have two classes of drugs, fibrates groups and statins groups.
- LDL is high when it is more than 160.
- HDL when less than 40 it must be increased, triglycerides more than 200 and cholesterol more than 200 or 240.

- **<u>Classification of drugs:-</u>**

1) Hydroxymethylglutaryl reductase (this enzyme is important for the synthesis of cholesterol in the liver or any cells) inhibitors:-

- blocks the synthesis of cholesterol in the liver, so,,,
  1) Decrease VLDL.
  2) Mainly decrease triglycerides in blood, because VLDL carries them.
  3) Increase LDL receptors due to decrease in the cholesterol in the cells.
  4) Decrease LDL in blood, because it is taken by the cells.
  5) Increase HDL.
- These are the main effects of inhibition of the cholesterol synthesis, this group like statin group.
-Studies have found that the first drug of choice of treatment of hyperlipidemic patients is statin group, The drugs are:-
  1) Lovastatin_40mg.
  2) Pravastatin_40mg.
  3) Simvastatin_20mg.
  4) Atrovastatin_10mg.
  5) Rosuvastatin_5mg.
- The most important drug that we use here is atrovastatin 10 mg.
- These drugs have different potency and different efficacy, they compared them by estimating which dose decreases LDL by 35%, so in case of lovastatin it is 40mg, pravastatin_40mg, simvastatin_20mg, atrovastatin_10mg, and rosuvastatin_5mg. so the most potent drug is rosuvastatin_5mg but it has a lot of inconvenient side effects, so now the mostly used drug is atrovastatin.

- If we want to decrease cholesterol up to 50%, they noted that this occur when simvastatin and atrovastatin are used at 80mg/day.
- So the amount of cholesterol(LDL) needed to be eliminated can be achieved when the drug concentration is increased to the maximum allowed daily dose. So if pt. has genetic primary hyperlipidemia, we can use drug at this concentration.

2) Bile acid sequestrant:-

- Cause decrease bile acids, so liver increase bile acids synthesis from cholesterol, so indirectly decrease cholesterol.
- The most important drug in this group is cholestramine and is used in large dose and inconvenient for the patient or used in combination(not used alone) with other drugs. In some pt. if there is no benefit from statin we add cholestramine to help it in reduction of cholesterol and inhibition of bile acid action.

3) LPL activator (fibrates):-

- Chlorifibrate and gemfibrozil.
- Benzafibrate and fenofibrate are the second generation.
- These drugs increase the activity of lipoprotein lipase, so increase the degradation of chylomicrone- but this is not important because TG in this case are dietary and can be decreased by decrease intake of lipid.
-The action of drug is important in VLDL conversion to IDL then LDL, so decrease triglycerides and increase HDL. So in pt. with isolated hypertriglyceridemia and have normal LDL, the drug of choice is fibrates. And in pt with hyperlipidemia and didn't benefit from statins we can add fibrates, so they can be used alone or in combination with other drugs.
- The effect of fibrates is increase HDL and decrease TG and increase LDL (side effect of gemfibrozil is increase in LDL but finofibrate from the second generation doesn't have this side effect) this depends on the activity of the drug, if the activity is high, it will increase the excess of LDL and will cause saturation to all the receptors and some

excess LDL will increase in the blood(Gemfibrozil is first generation increase LDL) ,but second generation fenofibrate doesn't increase LDL ,decrease TG and increase HDL.

4) Inhibitors of cholesterol absorption in the intestine:-

- isexinide is the only drug in this group, for dietary cholesterol.

5) Nicotinic acid or niacin:-

- increase the lipolysis, i.e. increase the degradation of free fatty acids and decrease protein adhesion, they are used only in combination.

-Statins are given at bed time, esp. lovastatin, pravastatin and simvastatin due to their short half life, except atrovastatin and rosuvastatin have long half life so not necessarily given at bed time, but it is better to give them at bed time to increase the efficacy and activity.

-The maximum synthesis of cholesterol is at midnight, and because the maximum activity of the drug is at midnight we give the drug at this time.

- **Side effect:-**

-They produce muscle pain and if combined with gemifibrocil cause myopathy.

- Myopathy can increase if we combined statins with enzyme inhibitors..... erythromycin, because they lead to inhibition of statin metabolism and increase their concentration leading the myopathy.

- Cholestramine, a lot of side effect and not convenient for the pt. so they are not used alone only in combination with other drugs.

- Fibrates:- first generation are taken before meal, and second generation are taken with meal

First drugs used in hyperlipidemia are statins.

- هذه الملخصات عباره عن اجتهاد شخصي لمجموعه من طلاب الطب البشري/عدن معتمدين على ما تم مراجعته او قراته وقد تفيد البعض منكم وللعلم ليس لها أي علاقه مباشره باي عضو من أعضاء الهيئة التعليمية في الكلية . زملائنا الأعزاء ان اصبنا فمن الله وان اخطانا فمن انفسنا ومن الشيطان ، نبقى بشرا نصيب ونخطئ، لذا يرجى الاشعار في حاله وجود أي ملاحظات عن طريق جروبنا في الفيس بوك او عبر ايميل الجروب.

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